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(54) **Process for producing optically active 2-hydroxy-4-arylbutyric acid or its ester, and intermediate therefor**

(57) Optically active acyloxysuccinic anhydride is reacted with an aromatic compound in the presence of a Lewis acid to produce an optically active 2-acyloxy-4-oxo-4-arylbutyric acid, which can then be converted into an optically active 2-acyloxy-4-arylbutyric acid by

catalytic reduction, and the latter compound hydrolyzed in the presence of an acid or an alkali to produce an optically active 2-hydroxy-4-arylbutyric acid, which can optionally be reacted with an alcohol in the presence of an acid to produce an optically active 2-hydroxy-4-arylbutyric acid ester.

## Description

### Field of the Invention

The present invention relates to a process for producing an optically active 2-hydroxy-4-arylbutyric acid or its ester, which is useful as an intermediate for synthesis of enalapryl or silazapryl which is known as an excellent anti-hypertensive agent; and especially, optically active 2-hydroxy-4-phenylbutyric acid or its ester.

### Background to the Invention

Known examples of a process for producing an optically active 2-hydroxy-4-phenylbutyric acid include:

- (i) a process in which racemic 2-hydroxy-4-phenylbutyric acid is used as a starting material and is subjected to an enzymatic reaction in the presence of an acylating agent to obtain the (R)-isomer (Agric. Biol. Chem. (1991), 55, 293),
- (ii) a process in which racemic 2-hydroxy-4-phenylbutyric acid is formed into a salt with an optically active amine, and this salt is resolved using a difference in solubility in a diastereomer (US-5,225,408),
- (iii) a process in which 2-oxo-4-phenylbutyric acid is asymmetrically reduced through an enzymatic reaction [J. Biotechnol., 24, 315 (1992)],
- (iv) a process in which 2-oxo-4-phenylbutyric acid is asymmetrically hydrogenated [Std. Surf. Sci. Catal., 78, 139 (1993)],
- (v) a process in which D-homophenylalanine is reacted with nitrous acid to form (R)-2-hydroxy-4-phenylbutyric acid (US 329,156), and
- (vi) a process in which benzalpyruvic acid is formed into (R)-2-hydroxy-4-phenyl-3-butenic acid using an L-proline-sodium boron hydride composite, and this butenic acid is then catalytically hydrogenated to form (R)-2-hydroxy-4-phenylbutyric acid [Japanese Laid-Open Patent Application (Kokai) No. 18,050/1992].

Known examples of a process for producing an optically active 2-hydroxy-4-phenylbutyric acid ester include:

- (vii) a process in which a racemic 2-hydroxy-4-phenylbutyric acid ester is subjected to an enzymatic reaction to hydrolyze the (S)-isomer alone and obtain an ester of the (R)-isomer [Japanese Laid-Open Patent Application (Kokai) No. 225,499/1989],
- (viii) a process in which a racemic 2-acyloxy-4-phenylbutyric acid ester is subjected to an enzymatic reaction to deacylate the (R)-isomer alone and obtain the (R)-hydroxy compound [Japanese Laid-Open Patent Application (Kokai) No.

247,100/1989],

(ix) a process in which a 2-oxo-4-phenylbutyric acid ester is asymmetrically reduced through an enzymatic reaction [Japanese Laid-Open Patent Application (Kokai) No. 328,984/1993],

(x) a process in which racemic 2-hydroxy-4-phenylbutyric acid is optically resolved and then esterified [J. Chem. Soc., Perkin Trans. 1, 1011 (1986)],

(xi) a process in which a 1-menthol ester of 2-oxo-4-phenylbutyric acid is synthesized, and then reduced [Tetrahedron Lett., 423 (1988)], and

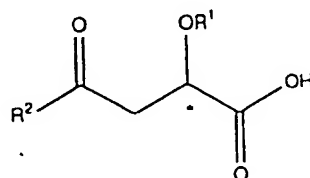
(xii) a process in which a 2-oxo-4-phenylbutyric acid ester is asymmetrically hydrogenated (EP 206993 and EP 564406).

However, processes (i), (ii), (vii), (viii) and (x) using the racemic 2-hydroxy-4-phenylbutyric acid ester as a starting material are problematic in that the yield does not exceed 50% in principle. Further, in processes (iii), (iv), (ix), (xi) and (xii) using 2-oxo-4-phenylbutyric acid or its ester as a starting material, the step of forming the 2-oxo-4-phenylbutyric acid ester is intricate, and the yield is not satisfactory. In process (v) using D-homophenylalanine as a starting material, the amino acid is itself not a natural-type amino acid, and its production cost is, therefore, high. Thus, this process is not practical. Still further, since process (vi) using benzalpyruvic acid as a starting material comprises two steps, it is intricate and entails a high cost.

### Summary of the Invention

The present inventors have found that when an optically active acyloxysuccinic anhydride, which can easily be formed from optically active malic acid, is used as a starting material and is reacted with an aromatic compound in the presence of a Lewis acid as a catalyst, an optically active 2-acyloxy-4-oxo-4-arylbutyric acid, which is a useful intermediate of an optically active 2-hydroxy-4-arylbutyric acid or its ester, can easily be obtained, and that this compound can be further subjected to reduction, deacylation and (optionally) esterification to obtain 2-hydroxy-4-aryl butyric acid or its ester.

According to a first aspect, the present invention provides a process for producing an optically active 2-acyloxy-4-oxo-4-arylbutyric acid represented by formula (II)



(II)

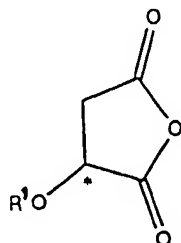
wherein

R<sup>1</sup> represents a linear, branched or cyclic aliphatic acyl group having from 2 to 7 carbon atoms which group may be substituted with a halogen atom, or an aromatic acyl group having from 7 to 11 carbon atoms,

R<sup>2</sup> represents an optionally substituted aryl group having from 4 to 10 carbon atoms, and

\* represents an asymmetric carbon atom,

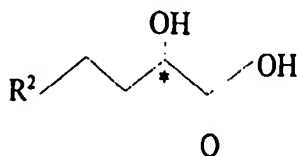
which comprises reacting optically active acyloxysuccinic anhydride represented by formula (I)



(I)

wherein R<sup>1</sup> and \* are as defined above with an optionally substituted aromatic compound having from 4 to 10 carbon atoms in the presence of a Lewis acid as a catalyst.

The present invention in a second aspect provides a process for producing an optically active 2-hydroxy-4-arylbutyric acid represented by formula (II)

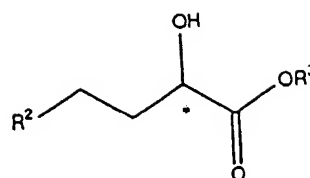


(II)

wherein

R<sup>2</sup> and \* are as defined in formula (II), which comprises subjecting an optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) to catalytic reduction of the carbonyl group in the 4-position and elimination of the acyl group.

The present invention in a third aspect provides a process for producing an optically active 2-hydroxy-4-arylbutyric acid ester represented by formula (IV)

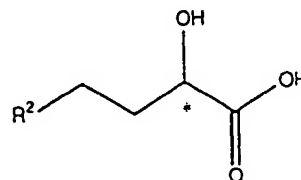


(IV)

wherein R<sup>2</sup> and \* are as defined in formula (II), and R<sup>3</sup> represents an optionally substituted, linear, branched or cyclic alkyl group having from 1 to 6 carbon atoms, or an aralkyl group having from 7 to 12 carbon atoms,

which comprises subjecting an optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) to catalytic reduction of the carbonyl group in the 4-position, elimination of the acyl group, and esterification with an optionally substituted, linear, branched or cyclic alkyl alcohol having from 1 to 6 carbon atoms or with an aralkyl alcohol having from 7 to 12 carbon atoms.

The present invention in a further aspect provides optically active 2-acyloxy-4-oxo-4-phenylbutyric acid represented by formula (V)



(V)

wherein

R<sup>1</sup> and \* are as defined in formula (II).

#### Detailed Description of the Invention

The first process of the present invention is described below.

In this process, optically active acyloxysuccinic anhydride of formula (I) is reacted with an optically substituted aromatic compound having from 4 to 10 carbon atoms in the presence of a Lewis acid as a catalyst to produce an optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II).

The acyl group (R<sup>1</sup>) in optically active acyloxysuccinic anhydride of formula (I), which is a starting material in this process, includes a linear, branched or cyclic aliphatic acyl group having from 2 to 7 carbon atoms, which group may be substituted with a halogen atom or the like, and an aromatic acyl group having from 7 to 11 carbon atoms. Specific examples thereof include an

acetyl group, a trifluoroacetyl group and a benzoyl group. The acetyl group is industrially preferable in view of the post-treatment and the cost.

The optically active acyloxysuccinic acid of formula (I) can easily be formed through the reaction of optically active malic acid and halogenated acyl and/or an acid anhydride. For example, optically active acetoxysuccinic anhydride can easily be formed by reacting optically active malic acid with acetic anhydride in the presence of acetyl chloride [J. Org. Chem., 53, 1040 (1988)].

The aromatic compound which is the other starting material for producing the desired optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) is an aromatic compound in a broad sense of the word. Examples of the aromatic compound include benzene, naphthalene, furan, thiophene, pyrrole, indole, and derivatives thereof. For example, in order to form an intermediate of enalapril which is one of the desired compounds in the present invention, benzene can be used.

Examples of the Lewis acid as a catalyst include anhydrous aluminum chloride, boron trichloride, and titanium tetrachloride. Anhydrous aluminum chloride is most preferable in view of the yield.

The conditions for the production of the desired optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) are not particularly limited so long as the desired compound is produced. For example, a reaction vessel is charged with optically active acyloxysuccinic anhydride of formula (I) and the aromatic compound in an amount which is equimolar to or larger than that of the compound of formula (I), preferably in an amount of from 1 to 10 mols per mol of the compound of formula (I). The solvent is added thereto to form a uniform solution. Then, the Lewis acid is added thereto in an amount of from 1 to 10 mols, preferably from 2 to 5 mols per mol of optically active acyloxysuccinic anhydride, and the mixture is stirred to produce the desired compound. When the amount of the aromatic compound based on optically active acyloxysuccinic anhydride is too small, the yield is reduced. When it is too large, this is problematic. Further, when the amount of the Lewis acid based on optically active acyloxysuccinic anhydride is too small, the yield is reduced. When it is too large, this is problematic.

The reaction can be conducted by first charging the Lewis acid and the solvent into a reaction vessel to form a solution or a suspension of the Lewis acid, and then adding optically active acyloxysuccinic anhydride and the aromatic compound. In this case, the amounts of the starting materials and the catalyst can be exactly the same as the above-mentioned amounts.

Any solvent can be used in this reaction (a kind of Friedel-Crafts reaction) so long as it does not adversely affect the reaction and the starting materials can be dissolved to an extent required for the reaction. Examples of the solvent include methylene chloride, dichloroethane, benzene, nitrobenzene, and a mixture thereof. The amount of the solvent is not particularly limited

so long as the reaction mixture can effectively be stirred. For example, it is usually from 1 to 100 parts by weight, preferably from 5 to 50 parts by weight per part by weight of optically active acyloxysuccinic anhydride as a starting material.

The reaction temperature is not particularly limited either so long as the reaction proceeds and the product is not decomposed. However, when the temperature is higher, side reaction occurs to decrease the reaction yield. It is, therefore, usually from -70°C to 30°C, preferably from -40°C to 0°C. When the temperature is too low, the reaction rate is decreased.

An aqueous solution of a mineral acid such as sulfuric acid, hydrochloric acid or the like is added to the reaction solution to stop the reaction, and the post-treatment is then conducted by a usual method in which layer separation, washing, extraction, concentration and crystallization are conducted in combination as required, whereby the desired optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) can easily be isolated. Usually, in the Friedel-Crafts reaction, a gum substance derived from aluminum is, in many cases, precipitated in the post-treatment step, making it hard to conduct the reaction. However, in the process of the present invention, almost no gum substance is precipitated, and the reaction proceeds quite well.

In the process of the present invention, the steric configuration of the optically active acyloxysuccinic anhydride used as the starting material becomes that of the resulting optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) as it is. As a starting material of an anti-hypertensive agent such as the above-mentioned enalapril or cilazapril, a 2-acyloxy-4-oxo-4-arylbutyric acid of a (R)-form which is obtained from starting (R)-malic acid is useful. However, when less costly (S)-malic acid is selected as a starting material, this (S)-malic acid is esterified or hydrolyzed in the same manner as (R)-malic acid (refer to Example 6) to form a 2-hydroxy compound, and this compound is converted into a compound having a leaving group such as a methanesulfonyloxy group or the like. Further, the compound is reacted with an acyloxy anion to be able to invert the steric configuration; this compound can be used as a starting material of the above-mentioned anti-hypertensive agent.

The second process of the present invention is described below.

In this process, the optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) which can be produced by the above-mentioned first process of the present invention is subjected to catalytic reduction of the carbonyl group in the 4-position and elimination of the acyl group.

With respect to the reduction, for example, the optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) is charged into the reaction vessel, and the solvent is added thereto to dissolve the compound of formula (II) therein. Then, the catalyst is added to the solution, and the catalytic reduction is conducted in a hy-

drogen atmosphere.

The solvent used in this reaction is not particularly limited so long as it does not adversely affect the reaction and the starting material can be dissolved therein to an extent required for the reaction. Examples of the solvent include water, lower alcohols such as ethanol, lower aliphatic acids such as acetic acid, lower esters such as ethyl acetate, ether-type solvents such as tetrahydrofuran, and a mixture thereof. A reaction accelerator such as hydrochloric acid, sulfuric acid or the like may be added thereto as required. The amount of the solvent is not particularly limited so long as the reaction mixture can effectively be stirred. For example, it is usually between 1 and 100 parts by weight, preferably between 5 and 50 parts by weight per part by weight of the optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II).

The catalyst to be used in the reduction is not particularly limited so long as the reaction can smoothly proceed. Examples of the catalyst include palladium, rhodium, ruthenium, platinum and nickel. These catalysts may be supported on carbon or the like, or contain water. The amount of the catalyst is not particularly limited so long as the desired reaction can be completed. For example, it is usually between 0.01 and 10 mols, preferably between 0.1 and 5 mols per 100 mols of the optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II).

The hydrogen pressure in the reduction is not particularly limited so long as the reaction can smoothly proceed. For example, it is usually between 1 and 150 kgf/cm<sup>2</sup>, preferably between 1 and 20 kgf/cm<sup>2</sup>.

The reaction temperature is not particularly limited so long as the reaction proceeds and the product is not decomposed. For example, it is usually between -20°C and 120°C, preferably between 0°C and 100°C.

After the completion of the reduction, the catalyst is removed through filtration, and the solvent is removed by distillation to obtain the optically active 2-acyloxy-4-arylbutyric acid in which the carbonyl group in the 4-position is reduced.

Subsequently, the acyl group of this optically active 2-acyloxy-4-arylbutyric acid can be eliminated by, for example, hydrolyzing an acyloxy moiety with an appropriate hydrolyzing agent such as an acid or an alkali to remove the acyl group. In this manner, the desired optically active 2-hydroxy-4-arylbutyric acid of formula (III) can be obtained.

The hydrolysis can be conducted, for example, after the completion of the above-mentioned reduction, by adding water and if required, a water-miscible organic solvent such as a lower alcohol, acetone or dioxane to a residue obtained by removing the catalyst and the solvent, and then further adding an acid or an alkali thereto.

The acid or the alkali to be used in the hydrolysis is not particularly limited so long as the reaction can smoothly proceed. Examples thereof include sulfuric acid, hydrochloric acid, sodium hydroxide and potassium hydroxide.

After the completion of the reaction, the post-treatment is conducted by a usual method in which concentration, extraction and washing are conducted in combination as required, and the product is purified through crystallization, distillation or the like, whereby the desired optically active 2-hydroxy-4-arylbutyric acid of formula (III) can easily be isolated.

The third process of the present invention is described below.

In this process, the optically active 2-acyloxy-4-oxo-arylbutyric acid of formula (II) which can be formed by the above-mentioned first process of the present invention is subjected to catalytic reduction of the carbonyl group in the 4-position, elimination of the acyl group, and esterification with an optionally substituted, linear, branched or cyclic alkyl alcohol having from 1 to 6 carbon atoms or with an aralkyl alcohol having from 7 to 12 carbon atoms, to produce the optically active 2-hydroxy-4-arylbutyric acid ester of formula (IV).

The reduction is conducted in exactly the same manner as in the above-mentioned second process of the present invention. The esterification is conducted by dissolving the optically active 2-acyloxy-4-arylbutyric acid obtained from the optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) in a solvent to be ordinarily used in the esterification, for example, ethanol in case of an ethyl ester, adding an acid catalyst to the solution, and heat-refluxing the mixture. The acyl group is decomposed in the presence of the solvent under the above-mentioned conditions simultaneously with the esterification, and the desired optically active 2-hydroxy-4-arylbutyric acid ester of formula (IV) can be produced.

The amount of the solvent is not particularly limited so long as the reaction mixture can efficiently be stirred. For example, it is between 1 and 100 parts by weight, preferably between 5 and 50 parts by weight per part by weight of the optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II).

The acid catalyst to be used in the esterification is not particularly limited so long as the reaction can smoothly proceed. Examples of the acid catalyst include sulfuric acid, methanesulfonic acid, p-toluenesulfonic acid and hydrogen chloride. The amount of the acid catalyst is not particularly limited so long as the desired reaction can be completed. For example, it is usually between 0.1 and 100 mols, preferably between 1 and 30 mols per 100 mols of the optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II).

After the completion of the esterification, the post-treatment is conducted by a usual method in which concentration, extraction and drying are conducted in combination as required, and the product is purified through crystallization and distillation, whereby the desired optically active 2-hydroxy-4-arylbutyric acid ester of formula (IV) can easily be isolated like its free acid of formula (III).

When the reduction is conducted in the solvent

which is used in the esterification, the reduction, deacylation and esterification can be conducted simultaneously to some extent.

The optically active 2-acyloxy-4-oxo-4-arylbutyric acid of formula (II) of the present invention is a novel compound.

Especially the compound in which the aryl group is a phenyl group and/or the asymmetric carbon gives the (R)-form is useful as an intermediate for synthesis of analapril or the like as stated above.

#### Examples

The present invention is illustrated more specifically by referring to the following Examples. However, the present invention is not limited thereto.

##### Example 1

Production of (R)-2-acetoxy-4-oxo-4-phenylbutyric acid:

(R)-acetoxy succinic anhydride (4.74 g) and 2.34 g of benzene were dissolved in 50 ml of methylene chloride, and the solution was cooled to -10°C. A suspension of 8 g of anhydrous aluminum chloride in 50 ml of methylene chloride was added to this solution in a dry argon atmosphere while being stirred carefully lest the temperature of the solution should exceed 0°C. The mixture was stirred for 22 hours while maintaining the temperature of the solution at between -3°C and 0°C, and 50 ml of 6-N hydrochloric acid were added thereto to stop the reaction.

The aqueous layer was separated, and the methylene chloride layer was washed with 50 ml of water. Then, methylene chloride was distilled off under reduced pressure. To the residue were added 50 ml of isopropyl acetate, and water separated was removed. Thereafter, isopropyl acetate was distilled off under reduced pressure to obtain 4.74 g of crude (R)-2-acetoxy-4-oxo-4-phenylbutyric acid as a light-yellow oily residue. When this crude product was allowed to stand at room temperature, it was crystallized. The thus-crystallized product was recrystallized from ether to give (R)-2-acetoxy-4-oxo-4-phenylbutyric acid as a white prism crystal.

$[\alpha]_D^{20} = -21.1^\circ$  (c = 1, ethanol)

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ,  $\delta$ ppm) : 2.12 (s, 3H), 3.55 (dd, 1H, J=3.9Hz), 3.66 (dd, 1H, J=7.8), 5.75 (q, 1H), 7.48 (m, 2H), 7.62 (m, 1H), 7.96 (m, 2H)

MS (ESI, m/z) : 237.5 (MH<sup>+</sup>), 259.5 (M+Na<sup>+</sup>), 495.4 (2M+Na<sup>+</sup>).

IR (KBr,  $\text{cm}^{-1}$ ) : 1760, 1702, 1688 (C=O).

mp : 118 - 121°C

##### Example 2

Production of (S)-2-acetoxy-4-oxo-4-phenylbutyric acid:

(S)-acetoxy succinic anhydride (15.81 g) and 23.43 g of benzene were dissolved in 150 ml of methylene chloride, and the solution was cooled to -20°C. Forty grams of anhydrous aluminum chloride were added to this solution in a dry argon atmosphere while being stirred carefully upon watching the increase in the temperature. The mixture was stirred for 6 hours while maintaining the temperature of the solution at -20°C. Thereafter, 100 ml of 1-N hydrochloric acid were added thereto carefully lest the temperature should exceed 30°C, and the reaction was stopped.

The stirring was continued at room temperature until all the solids precipitated were dissolved. Then, the aqueous layer was separated, and methylene chloride was distilled off under reduced pressure. The residue was dissolved in 150 ml of isopropyl acetate, and washed with water. Subsequently, isopropyl acetate was distilled off under reduced pressure to obtain 19.86 g of crude (S)-2-acetoxy-4-oxo-4-phenylbutyric acid as a light yellow solid. This product was recrystallized from a mixed solution of ethanol and tert-butylmethyl ether to give (S)-2-acetoxy-4-oxo-4-phenylbutyric acid as a white prism crystal.

##### Example 3

Production of (R)-2-acetoxy-4-oxo-4-phenylbutyric acid:

(R)-acetoxy succinic anhydride (47.44 g) and 35.15 g of benzene were dissolved in 450 ml of methylene chloride, and the solution was cooled to -16°C. Anhydrous aluminum chloride (120.00 g) was added to this solution while being stirred carefully upon watching the increase in the temperature. The mixture was stirred for 6 hours while maintaining the temperature of the solution at -16°C. Thereafter, 300 ml of 1-N hydrochloric acid were added thereto carefully lest the temperature should exceed 20°C, and the reaction was stopped.

The stirring was continued at room temperature until all the solids precipitated were dissolved. Further, 100 ml of isopropyl acetate were added thereto, and the mixture was stirred for a short period of time. Then, the aqueous layer was separated, and the organic layer was concentrated under reduced pressure. To the resulting slurry were added 450 ml of isopropyl acetate. The mixture was stirred until all the crystals were dissolved, and was then washed with water. The isopropyl acetate layer was concentrated under reduced pressure until the amount of the solution reached approximately 300 ml, and n-hexane was added thereto in the same volume as the concentrate. The mixture was cooled to 5°C, and was stirred overnight at this temperature. The slurry was

separated, and dried to obtain 62.70 g of (R)-2-acetoxy-4-oxo-4-phenylbutyric acid as a white crystal. The HPLC analysis of the resulting product revealed that the purity (measured value based on a standard sample) was 100.8% and the optical purity was 100%ee.

#### Example 4

Production of (S)-2-acetoxy-4-oxo-4-phenylbutyric acid:

Example 3 was repeated except that (R)-acetoxy-succinic anhydride was replaced with (S)-acetoxy-succinic anhydride to obtain 59.53 g of (S)-2-acetoxy-4-oxo-4-phenylbutyric acid as a white crystal. The HPLC analysis of the resulting product revealed that the purity (measured value based on a standard sample) was 98.58% and the optical purity was 100%ee.

#### Example 5

Production of ethyl (R)-2-hydroxy-4-phenylbutyrate:

Sixty grams of (R)-2-acetoxy-4-phenylbutyric acid were dissolved in 380 ml of ethanol, and 1.31 g of sulfuric acid and 5.41 g of 5-% palladium on carbon (water content 50%) were added thereto. The mixture was stirred in a hydrogen atmosphere at 20°C for 20 hours. Palladium on carbon was separated through filtration, and 2.62 g of sulfuric acid were further added to the solution. The mixture was heat-refluxed for 16 hours. The solvent was distilled off under reduced pressure, and 380 ml of ethanol were added again to the residue. The mixture was further heat-refluxed for 4 hours.

After the completion of the reaction, ethanol was distilled off under reduced pressure. To the resulting oily residue were added 500 ml of isopropyl acetate. The mixture was washed with 250 ml of a 5-% sodium bicarbonate aqueous solution and then with 250 ml of water, and was concentrated under reduced pressure to obtain an isopropyl acetate solution of ethyl (R)-2-hydroxy-4-phenylbutyrate. The HPLC analysis of the product revealed that the amount of ethyl (R)-2-hydroxy-4-phenylbutyrate was 48.02 g, the purity (area percentage) thereof was 99.8%, and the optical purity thereof was 100%ee.

#### Example 6

Production of ethyl (S)-2-hydroxy-4-phenylbutyrate:

(S)-2-acetoxy-4-oxo-4-phenylbutyric acid (16.40 g) was dissolved in 100 ml of ethanol, and 0.35 g of sulfuric acid and 1.55 g of 5-% palladium on carbon (water content 50%) were added thereto. The mixture was stirred in a hydrogen atmosphere at 20°C for 40 hours. Palladium on carbon was separated through filtration, and 0.71 g of sulfuric acid were further added to the solution.

The mixture was heat-refluxed for 16 hours. The solvent was distilled off under reduced pressure, and 100 ml of ethanol were added again to the residue. The mixture was further heat-refluxed for 4 hours.

After the completion of the reaction, ethanol was distilled off under reduced pressure. To the resulting oily residue were added 140 ml of isopropyl acetate. The mixture was washed with 70 ml of a 5-% sodium bicarbonate aqueous solution and then with 70 ml of water, and was concentrated under reduced pressure to obtain an isopropyl acetate solution of ethyl (S)-2-hydroxy-4-phenylbutyrate. The HPLC analysis of the product revealed that the amount of ethyl (S)-2-hydroxy-4-phenylbutyrate was 13.11 g, the purity (area percentage) thereof was 99.2%, and the optical purity thereof was 100%ee.

#### Example 7

Production of (R)-2-hydroxy-4-phenylbutyric acid:

(R)-2-acetoxy-4-oxo-4-phenylbutyric acid (2.36 g) was dissolved in 15 ml of acetic acid, and 0.21 g of 5-% palladium on carbon (water content 50%) were added thereto. The mixture was stirred in a hydrogen atmosphere at 60°C for 24 hours. Palladium on carbon was separated by filtration, and the solvent was then distilled off. Thirty milliliters of 1-N hydrochloric acid were added to the resulting (R)-2-acetoxy-4-phenylbutyric acid, and the mixture was heat-refluxed for 3 hours while being stirred.

The reaction solution was stirred in an ice bath while being cooled to precipitate (R)-2-hydroxy-4-phenylbutyric acid as a white crystal. This product was collected by filtration, and dried. The amount of (R)-2-hydroxy-4-phenylbutyric acid dried was 1.45 g, and the optical purity thereof was 100%ee.

#### Example 8

Production of ethyl (R)-2-hydroxy-4-phenylbutyrate:

One gram of crude (R)-2-acetoxy-4-oxo-4-phenylbutyric acid obtained in Example 1 was dissolved in 10 ml of acetic acid, and 0.36 g of 5-% palladium on carbon (water content 50%) were added thereto. The mixture was stirred in a hydrogen atmosphere at 70°C for 24 hours. Palladium on carbon was separated through filtration, and acetic acid was distilled off under reduced pressure. The residue containing (R)-2-acetoxy-4-phenylbutyric acid was dissolved in 25 ml of ethanol, and 4 droplets of sulfuric acid were added thereto as a catalyst. The mixture was heat-refluxed for 6 hours. Subsequently, ethanol was distilled off under reduced pressure, and 25 ml of ethanol were added again thereto. The mixture was further heat-refluxed for 5 hours.

After the completion of the reaction, ethanol was distilled off under reduced pressure. To the resulting oily

residue were added 30 ml of isopropyl acetate. The mixture was washed with 25 ml of a 5-% sodium bicarbonate aqueous solution and then with 25 ml of water, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was separated through filtration, and isopropyl acetate was then distilled off under reduced pressure to obtain 0.83 g of an oily residue containing ethyl (R)-2-hydroxy-4-phenylbutyrate. The HPCL analysis of this residue revealed that the amount of ethyl (R)-2-hydroxy-4-phenylbutyrate was 64.5%.

#### Example 9

Production of (R)-2-hydroxy-4-phenylbutyric acid:

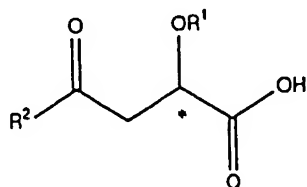
One gram of crude (R)-2-acetoxy-4-oxo-4-phenylbutyric acid was reduced in the same manner as in Example 8 to obtain (R)-2-acetoxy-4-phenylbutyric acid. To this were added 15 ml of 1-N hydrochloric acid, and the mixture was heat-refluxed for 2 hour while being stirred.

When the reaction solution was analyzed through HPLC, it was found that 0.54 g of (R)-2-hydroxy-4-phenylbutyric acid were formed. The reaction solution was hot-filtered to remove small amounts of insoluble matters. Then, the residue was cooled in an ice bath to precipitate (R)-2-hydroxy-4-phenylbutyric acid as a white crystal. This product was collected through filtration, and dried. The amount of (R)-2-hydroxy-4-phenylbutyric acid dried was 0.45 g.

In accordance with the process of the present invention, a high-purity, optically active 2-hydroxy-4-arylbutyric acid or its ester can easily be produced in quite high yield. Therefore, the process of the present invention is an extremely advantageous process for producing the optically active 2-hydroxy-4-arylbutyric acid or its ester which is useful as an intermediate in the preparation of optically active 2-hydroxy-4-arylbutyric acid.

#### Claims

1. A process for producing an optically active 2-acyloxy-4-oxo-4-arylbutyric acid represented by formula (II)



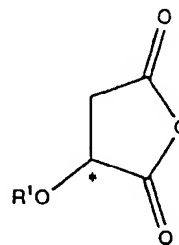
(II)

wherein

R¹ represents a linear, branched or cyclic aliphatic acyl group having from 2 to 7 carbon atoms which group may be substituted with a halogen atom, or an aromatic acyl group having from 7 to 11 carbon atoms,

R² represents an optionally substituted aryl group having from 4 to 10 carbon atoms, and \* represents an asymmetric carbon atom,

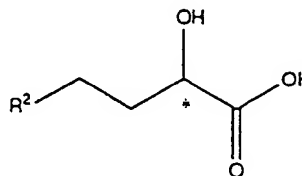
which comprises reacting optically active acyloxy-succinic anhydride represented by formula (I)



(I)

wherein R¹ and \* are as defined above with an optionally substituted aromatic compound having from 4 to 10 carbon atoms in the presence of a Lewis acid as a catalyst.

2. The process of claim 1, wherein R¹ is an acetyl group.
3. The process of claim 1 or claim 2, wherein the Lewis acid is anhydrous aluminum chloride.
4. A process for producing an optically active 2-hydroxy-4-arylbutyric acid represented by formula (III)



(III)

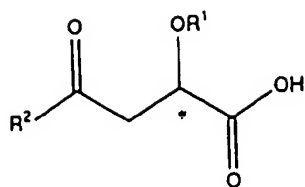
wherein

R² represents an optionally substituted aryl group having from 4 to 10 carbon atoms, and \* represents an asymmetric carbon atom,

which comprises subjecting an optically active 2-acyloxy-4-oxo-4-arylbutyric acid represented by



formula (II)



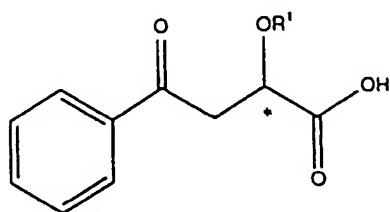
(II)

wherein

R<sup>1</sup> represents a linear, branched or cyclic aliphatic acyl group having from 2 to 7 carbon atoms which group may be substituted with a halogen atom, or an aromatic acyl group having from 7 to 11 carbon atoms, and R<sup>2</sup> and \* are as defined above

to catalytic reduction of the carbonyl group in the 4-position and elimination of the acyl group.

5. A process of claim 4 which includes the additional step of esterification with an optionally substituted, linear, branched or cyclic alkyl alcohol having from 1 to 6 carbon atoms or with an aralkyl alcohol having from 7 to 12 carbon atoms to produce an optically active 2-hydroxy-4-arylbutyric acid ester.
6. The process of any one of the preceding claims, wherein R<sup>2</sup> is a phenyl group.
7. The process of any one of the preceding claims, wherein the compounds of formulas (I), (II) and (III) are all (R)-isomers.
8. Optically active 2-acyloxy-4-oxo-4-phenylbutyric acid represented by formula (V)



(V)

wherein

R<sup>1</sup> represents a linear, branched or cyclic aliphatic acyl group having from 2 to 7 carbon

atoms which group may be substituted with a halogen atom, or an aromatic acyl group having from 7 to 11 carbon atoms, and \* represents an asymmetric carbon atom.

9. The compound of claim 8, wherein R<sup>1</sup> is an acetyl group.
10. The compound of claim 8 or 9 which is a (R)-isomer.



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number  
EP 96 30 6057

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,P	DE-A-195 03 926 (CHEMIE LINZ DEUTSCHLAND GMBH 1) 8 August 1996 * the whole document *	4-10	C07C69/007 C07C69/157 C07C51/377 C07C67/293
A	GB-A-2 210 364 (ICI PLC) 7 June 1989 * page 6, line 15 - line 20 *	1-10	
A	EP-A-0 329 156 (KURARAY CO) 23 August 1989	1-10	
A	EP-A-0 280 285 (MERRELL DOW PHARMA) 31 August 1988	1-10	
A	PATENT ABSTRACTS OF JAPAN vol. 018, no. 075 (C-1163), 8 February 1994 & JP-A-05 286890 (TORAY IND INC), 2 November 1993, (See also Derwent Abstract 93-383015) * abstract *	1-10	
A	PATENT ABSTRACTS OF JAPAN vol. 015, no. 472 (C-0889), 29 November 1991 & JP-A-03 200739 (DAICEL CHEM IND LTD), 2 September 1991, (see also Derwent Abstract 91-300250) * abstract *	1-10	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07C
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 31 October 1996	Examiner Janus, S
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p>			

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